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EXAMINER	
REDDIG, PETER J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,143	JENKINS, JOHN	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *4-6,10,14,15, 17, and 19-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-9,11-13,16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed October 15, 2007 in response to the Office Action of July 11, 2007 is acknowledged and has been entered.

2. In the previous Election filed May 7, 2007 Applicants elected with traverse Group I, claims 1-18, and the species compounds that bind to HSP90 and inhibit its activity, compounds that bind to TOPO II and inhibit its activity, cancer treatment, and solid tumors.

In the Election filed October 15, 2007 Applicants elected with traverse the species Geldanamycin or a derivative or analogue thereof/17-AAG, a Podophyllotoxin and derivatives and analogues thereof, etoposide/VP-16, and solid tumors of the lung is acknowledged.

Applicants argue that that the unifying inventive feature is that agents that attenuate Topo II activity may be combined with a second agent that inhibits HSP90 and have improved synergistic effects on cancer treatment not previously shown or taught by the prior art.

Applicant's arguments have been carefully considered, but have not been found persuasive because Applicant is arguing a limitation, synergy, not found in the claims. It is noted, however, that Münster et al. citation does show synergy in between doxorubicin and 17-AAG, see figure 6 and the Discussion.

Applicants argue that that the prior art reference cited by the Examiner, Münster et al. (Clinical Cancer Res. 2001,7:2228-2236, IDS) ("Münster "), does not show or teach the inventive unifying feature common to the inventions of Groups 1-13, that Topo II and HSP90 interact such that a combination of agents that specifically inhibit these individual protein has a synergistic effect. Although Münster discloses that ansamycin antibiotics such as 17-AAG (an HSP90 inhibitor) and doxorubicin may be combined, nowhere in Münster is the term

"topoisomerase II" used or the effect of either of these agents on Topo II described. Even though doxorubicin has been shown to inhibit Topo II, which is critical to DNA function, its effect on Topo II is not disclosed nor discussed in Münster. Rather, Münster simply describes the effect of these agents on apoptosis (studied by looking at the nuclei) and does not show synergy in terms of cell death or proliferation. There is no suggestion that any of the effects are related to the interaction between HSP90 and Topo II.

Applicant's arguments have been carefully considered, but have not been found persuasive. Applicant is arguing limitations, such as synergy and interaction between HSP90 and Topo II, which are not found in the claims and thus are not relevant to special technical feature of the invention. Although Münster does not specifically teach that doxorubicin modulates topoisomerase II, Applicant admits on the record that Doxorubicin inhibits DNA topoisomerase II. Thus, although doxorubicin may have other functions, it would inherently modulate topoisomerase II when added with 17-AAG.

Applicants argue that a skilled person may consider Münster to relate to the study of HSP90 modulated signaling pathways (i.e., RB pathways). It is well known that HSP90 inhibitors are effective in chemotherapy because they modulate signaling pathways. As such, a skilled person might conclude that doxorubicin may not be effective in chemotherapy because it is modulating Topo II (which is not a mediator of signal transduction). Accordingly, Münster does not show or teach the unifying feature of the present invention, namely, the modulation of Topo II.

Applicant's arguments have been carefully considered, but have not been found persuasive because Applicant admits on the record that Doxorubicin inhibits DNA

topoisomerase II. Thus, although doxorubicin may have other functions, it would inherently modulate topoisomerase II when added with 17-AAG. Furthermore, Münster et al. demonstrates synergy in between doxorubicin and 17-AAG, see figure 6 and the Discussion, and the effectiveness of doxorubicin for chemotherapy is well known in the art.

Thus the technical feature linking the inventions of Groups 1-13 does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

3. Claims 1-33 are pending.

4. Claims 4-6, 10, 14, 15, 17 and 19-33 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

5. Claims 1-3, 7-9, 11-13, 16 and 18 as drawn to compounds that bind to Topo II and inhibit its activity, compounds that bind to HSP90 and inhibit its activity, Geldanamycin or a derivative or analogue thereof/17-AAG, a Podophyllotoxin and derivatives and analogues thereof, which is etoposide/VP-16, and solid tumors of the lung are currently under consideration.

Information Disclosure Statement

6. The information disclosure statement is objected to because there is no identification of the source of the C1 reference and the authorship of reference C2 is incorrect.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 7-9, 11-13, 16 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 7-9, 11-13, 16 and 18 are indefinite because they lack a positive process step that clearly relates back to the preamble, e.g. whereby a cancer cell is treated.

Regarding claims 2 and 7, the phrase "including competitive and allosteric inhibitors" renders the claim(s) indefinite because it cannot be determined whether or not the phrase "including competitive and allosteric inhibitors" is meant to limit the claim to competitive and allosteric inhibitors, thus the scope of the claim cannot be ascertained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue

experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 18 is drawn to the method of claim 1 wherein chemotherapy is for prophylactic treatment.

It is noted that the term prophylactic is understood in the art to mean a medication or a treatment designed and used to prevent a disease from occurring(see http://www.medterms.com) thus, it is assumed for examination that limitations drawn to prophylactic treatment of cancer are in fact drawn to methods of preventing cancer.

The specification teaches that Topoisomerase II (Topo II) is required for the viability of all eukaryotic cells and plays important roles in DNA replication, recombination, chromosome segregation and the maintenance of the nuclear scaffold, see p. 2, 4th para.

The specification teaches that the Heat Shock Protein 90 (HSP90) consists of a highly conserved, 25 kDa N-terminal domain connected to a highly conserved, 55 kDa C-terminal region by a 'charged linker', which is variable in both length and composition among species and isoforms. The eukaryotic HSP90s are essential and ubiquitous molecular chaperones with key roles in the folding, activation and assembly of a range of client proteins typically involved in signal transduction, cell cycle control or transcriptional regulation, p.4 1st para.

The specification teaches that the combinations of VP16/etposide with 17-AAG or geldanamycin, produces synergistic toxicity in HCT-116 colon carcinoma cell lines, see Example 2,

Figs. 4-14. The specification teaches that VP-16/etoposide and Geldanamycin can cause significant reduction in HCT-116 tumor growth in a nude mouse tumor model, see Example 3, and figure 16.

The teachings of the specification do not enable one of skill in the art to use the method of claim 1 for the prophylactic treatment of lung cancer or any cancer because the neither the specification nor the art of record provides guidance or exemplification on using the claimed method for the prophylactic treatment, that is prevention, of lung cancer or any cancer. Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations, which have been successfully pre-screened and are predisposed to particular types of cancer or have had cancer. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and link those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing working examples, which are not disclosed in the specification

With regards to the prophylactic treatment of cancer comprising administering etoposide and geldanamycin or a derivative or analogue thereof, the specification does not disclose sufficient guidance or objective evidence that such a chemotherapeutic combination would predictably prevent the formation of lung cancer or any cancer in a subject. The prevention of cancer is highly unpredictable. The majority of studies suggest that the essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in

advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. Further, such studies require the appropriate experimental models for analyzing chemo- or immunoprevention. For example, Byers, T. (CA Journal, Vol. 49, No. 6, Nov/Dec. 1999) teaches that randomized controlled trials are commonly regarded as the definitive study for proving causality (1st col., p.358), and that in controlled trials the random assignment of subjects to the intervention eliminates the problems of dietary recalls and controls the effects of both known and unknown confounding factors. Further, Byers suggests that chemo-preventative trials be designed "long-term" such that testing occurs over many years (2nd col., p. 359). The specification is devoid of any models or experimental analysis that reasonably suggests that the claimed method would predictably prevent the formation of cancers in a subject. This, combined with the state of the art of preventing cancer, suggests that undue experimentation would be required to practice the invention as broadly claimed.

Additionally the specification does not define the individuals at risk or how to identify them, nor is there is teaching in the specification as to when the method is to be initiated. Certainly the majority of the population of the United States has been inadvertently exposed to carcinogenic substances, which would be expected to lead to cancers. Clearly not all of these individuals or even the majority of these individuals will develops cancers associated with the exposure to carcinogens and it is not clear how the claimed method would be used for these individuals, in particular because Holland-Frei (Cancer Medicine 6, 2003, BC Decker, 1-6) teaches that there are several toxicities associated with etoposide administration including myelosuppression, which is the major toxicity associated with the administration of etoposide, allergic reactions, fever, bronchospasm, hypotension, nausea, vomiting, and mucositis and

Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61, IDS) teach that Geldanamycin has proved to be too hepatotoxic for clinical use, see p. s57, left-col.

The undeveloped nature of the art of identifying individuals at risk for a given cancer is exemplified by Cotterchio et al, 2000, Chronic Diseases in Canada, (Electronic Version downloaded from www.phac-aspc.gc.ca/publicat/cdic-mcc/21-2/f_e.html). Drawn to colorectal cancer it is relevant to the unpredictability in the art of identifying patients at risk for developing cancer. Cotterchio et al. reveal that the reference is the first population-based family colorectal cancer registry developed within Canada and since this is a novel undertaking, there are no published reports with which to compare the data (see discussion, para 1). The reference specifically states that a high response rate is important in order to ensure that the families in the registry are representative of the population from which they are selected. However, obtaining high response rates in genetic family studies of colorectal cancer is especially challenging because of the time commitment required to complete the many phases of the data collection, issues of confidentiality and the high mortality rate among the cancer cases (see discussion, para 1). The reference specifically teaches that future research is needed to identify methods of overcoming these barriers to participation. Further the reference teaches that response bias arising from differences in characteristics between participants and non-participants is always a concern in epidemiologic studies when response rates are low, as it may lead to biased estimates of prevalence and association. Finally, in a review of a study for methods for determining risk of developing colorectal cancer wherein the reference concludes that the study offers exciting opportunities for the study of genetic and environmental factors associated with colorectal cancer as well as providing a source for the development of chemoprevention trials, cohort studies and

gene discovery projects. However, the reference neither teaches nor suggests how to identify which patients are at risk and should be candidates for any particular method of prophylactic treatment of lung cancer or any cancer or when to begin these protocols. Based on the information in this reference, it is clear that the assessment of patient risk is a developing but not a well-established art.

Furthermore, Martin et al (Journal of the National Cancer Institute, 92:1126-1135) in another study drawn to identifying patients at risk for developing neoplasia teaches that it is hoped that identification of genetic and environmental factors that contribute to the development of breast cancer will enhance prevention effects. Although drawn to breast cancer, it is relevant to the unpredictability in the art of identifying patients at risk for cancer. The reference reviews the state of the art of breast cancer genetic components of susceptibility to breast cancer from the standpoint of both human genetics and rat models (see abstract). The reference specifically states that despite numerous studies published to date, the role of modifier genes, apparently those involved in the development of sporadic neoplasia in breast cancer susceptibility remains to be elucidated. The resolution of ambiguous results will require further carefully designed studies with sufficient sample sizes to detect small effects. The reference concludes that great strides have been made in determining the disease etiology, but that further investigation is necessary and that these studies will be crucial to evaluate the importance of new genes involved in breast cancer etiology so that scientists can define better therapies and cancer prevention (p. 1132, col 1). It is clear from the teachings of this reference that the art of identifying an individual at risk of neoplasia is a developing, but as yet undeveloped art. The reference provides no guidance on

how to determine which patients are at risk or when to administer treatment in order to inhibit the neoplasia for which the individual is at risk.

Thus, if one cannot predictably identify the patient at risk for cancer or know when to begin treatment with etoposide and geldanamycin or a derivative or analogue thereof for the prophylactic treatment of lung or any other cancer, one of skill in the art would not how to use the claimed method for prophylactic treatment of cancer.

Given the unpredictability of tumor prevention, given the unpredictability of identifying patients that are in need of prophylactic lung cancer treatment or any prophylactic treatment and given the known toxicities of etoposide and geldanamycin or a derivative or analogue thereof, which would hinder their use for prophylactic treatment of subjects who are not currently presenting with a disease, one of skill in the art would not know how to make and use the invention as claimed. Thus, undue experimentation would be required to make and use the method as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the

invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

9. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph claims 1-3, 7-9, 11-13, 16 and 18 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of administering chemotherapy *in vitro* by administering Geldanamycin or a derivative or analogue thereof or 17-AAG and etoposide/VP-16 or for a method of administering chemotherapy by administering 17-AAG and etoposide/VP-16 for the treatment of lung cancer *in vivo* by attenuating Topo II activity and inhibiting HSP 90 activity, does not reasonably provide enablement for administering Geldanamycin or a derivative or analogue thereof and podophyllotoxin and derivatives and analogues thereof for the treatment of lung cancer by attenuating Topo II activity and inhibiting HSP 90 activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of administering chemotherapy, comprising administering a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is podophyllotoxin and derivatives and analogues thereof, which is etoposide/VP16, and administering second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is Geldanamycin or a derivative or analogue thereof or 17-AAG, wherein the first agent and the second agent are administered either contemporaneously or sequentially.

Given that the specification teaches that by "chemotherapy" we mean treatment of cells to cause a targeted cell death and chemotherapy is required in cancer treatment where it is desirable to target transformed cells, see page 2, 3rd paragraph. This means that claimed method reads on treatment of cells in vitro, other than claims specifically drawn to cancer treatment, or for in vivo cancer treatment with any of the broadly claimed compounds in combination with each other.

The specification teaches that Topoisomerase II (Topo II) is required for the viability of all eukaryotic cells and plays important roles in DNA replication, recombination, chromosome segregation and the maintenance of the nuclear scaffold, see p. 2, 4th para.

The specification teaches that the Heat Shock Protein 90 (HSP90) consists of a highly conserved, 25 kDa N terminal domain connected to a highly conserved, 55 kDa C-terminal region by a 'charged linker', which is variable in both length and composition among species and isoforms. The eukaryotic HSP90s are essential and ubiquitous molecular chaperones with key roles in the folding, activation and assembly of a range of client proteins typically involved in signal transduction, cell cycle control or transcriptional regulation, p.4 1st para.

The specification teaches that the combinations of VP16/etposide with 17-AAG or geldanamycin, produces synergistic toxicity in HCT-116 colon carcinoma cell lines, see Example 2, Figs. 4-14. The specification teaches that VP-16/etoposide and Geldanamycin can cause significant reduction in HCT-116 tumor growth in a nude mouse tumor model, see Example 3, and figure 16.

The state of the art is such that Holland-Frei (Cancer Medicine 6, 2003, BC Decker) teaches that etoposide is approved for the treatment of small cell lung cancer and testicular cancer in the United States. Additionally, Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61, IDS) teaches that 17-AAG in combination with taxol reduced tumor growth and increased survival in mice bearing small cell lung tumors, see p. S59 left. col.

One cannot extrapolate the teachings of the specification to the scope of the claims because 1) Geldanamycin has been found to be too toxic for in vivo use in the clinical setting 2) Podophyllotoxin does not attenuate topoisomerase II activity or bind to topo II and inhibits its activity 3) the art of cancer therapeutic development is unpredictable.

1) As drawn to Geldanamycin, Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61, IDS) teach that Geldanamycin has proved to be too hepatotoxic for clinical use, see p. s57, left-col. Thus, given that Geldanamycin is too hepatotoxic for clinical use, although activity is observed with geldanamycin against colon tumors in vivo in combination with etoposide, one of skill in the art could not predictably use Geldanamycin for a method of administering chemotherapy in vivo with a reasonable expectation of success without undue experimentation.

2) As drawn to Podophyllotoxin, Holland-Frei (Cancer Medicine 6, 2003, BC Decker) teaches that podophyllotoxin is an anti-microtubule that requires a structural change to confer its Topo II poisoning activity. Given that podophyllotoxin is an anti-microtubule agent and does not affect Topo II activity, undue experimentation would be required to use podophyllotoxin as an agent that attenuates Topo II activity or binds and inhibits Topo II activity for the claimed method of administering chemotherapy.

3) As drawn to the unpredictability of cancer therapeutic development in particular, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para.

Given the above, given the known toxicity of Geldanamycin, given that podophyllotoxin does not attenuate topo II activity, and given the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with

the invention claimed, no one skilled in the art would accept the assertion that Geldanamycin or any derivative or analogue of Geldanamycin, other than 17-AAG, in combination with Podophyllotoxin, and derivative and analogues thereof, other than etoposide/VP-16, would be effective for treatment of lung cancer in vivo by attenuation of topo II activity and HSP 90 activity, based only on examples and guidance provided in the specification without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will

function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

10. Claims 1-3, 7-9, 11-13, 16 and 18 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-3, 7-9, 11-13, 16 and 18 are broadly drawn to a method of administering chemotherapy, comprising administering a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is podophyllotoxin and derivatives and analogues thereof and administering second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is Geldanamycin or a derivative or analogue thereof, wherein the first agent and the second agent are administered either contemporaneously or sequentially.

The state of the art is such that it is well know in the art that identifying novel chemotherapeutics is unpredictable. In particular, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61, IDS) teach that although Geldanamycin binds and inhibits HSP90 it has proved to be too hepatotoxic for clinical use, see p. s57, left-col. Thus, given the above, it is

clear that in the cancer therapeutic arts an adequate written description is essential for one of skill in the art to make and use the claimed invention and it is clear that the specification does not provide a written description of the broadly claimed invention for the reasons set forth below.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative

number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin that can be used in a method of administering chemotherapy, per Lilly by structurally describing a representative number of

first agents that attenuate Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin and second agents that inhibit HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin that can be used in a method of administering chemotherapy, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin that can be used in a method of administering chemotherapy, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin, other than etoposide and teniposide, and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin, other than 17-AAG, that can be used in a method of administering chemotherapy, nor does the specification provide any partial structure of a first agent that

attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin, other than etoposide and teniposide, and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin, other than 17-AAG, that can be used in a method of administering chemotherapy, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses etoposide, teniposide, and 17-AAG, this does not provide a description of a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin that can be used in a method of administering chemotherapy that would satisfy the standard set out in Enzo.

The specification also fails to describe a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin that can be used in a method of administering chemotherapy by the test set out in Lilly. The specification describes only etoposide, teniposide, and 17-AAG. Therefore, it necessarily fails to describe a "representative number" of a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or

analogue of Geldanamycin that can be used in a method of administering chemotherapy. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin that can be used in a method of administering chemotherapy that is required to practice the claimed invention or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention. Since the specification fails to adequately describe or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention that is the broadly claimed a first agent that attenuates Topo II activity by binding to Topo II and inhibiting its activity, wherein that agent is a derivative or an analogues of podophyllotoxin and a second agent that inhibits HSP90 activity attenuates HSP90 activity by binding to HSP90 and inhibiting its activity, wherein the agent is a derivative or analogue of Geldanamycin that can be used in a method of administering chemotherapy, it also fails to adequately describe the claimed method or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-3, 7-9, 11-13, 16 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bilodeau et al. (US Patent No. 6,245,759, June 12, 2001) as evidenced by Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61, IDS),Holland-Frei (Cancer Medicine 6, 2003, BC Decker), and Medline Plus (http://www.nlm.nih.gov/medlineplus/ency/article/007194.htm).

The claims are drawn to:

1. A method of administering chemotherapy comprising: administering a first agent that attenuates Topoisomerase H (Topo II) activity; and administering a second agent that inhibits Heat Shock Protein 90 (HSP90) activity, wherein the first agent and the second agent are administered either contemporaneously or sequentially, and the first agent is selected from the group consisting of a Podophyllotoxin and derivatives and analogues thereof.

2. The method of claim 1 wherein the first agent is a compound selected from the group consisting of: (i) compounds that bind to Topo II and inhibit its activity, including competitive inhibitors and allosteric inhibitors.

3. The method of claim 1 wherein the first agent is selected from the group consisting of etoposide (VP16).

7. The method of claim 1 wherein the second agent is a compound selected from the group consisting of: (i) compounds that bind to Hsp90 and inhibit its activity, including competitive inhibitors and allosteric inhibitors.

8. The method of claim 7 wherein the second agent is Geldanamycin or a derivative or analogue thereof.

9. The method of claim 8 wherein the second agent is 17-Allylamino, 17-

demethoxygeldanamycin (17AAG).

11. The method of claim 1 wherein the chemotherapy is for cancer treatment.

12. The method of claim 11 wherein the chemotherapy is for the treatment of solid tumours.

13. The method of claim 12 wherein the chemotherapy is for the treatment of small cell and non-small cell lung cancer.

16. The method of claim 11 wherein the first agent is etoposide and the chemotherapy is used in the treatment of cancers selected from the group consisting of: Non-small Cell Lung Cancer and Small Cell Lung Cancer.

18. The method of claim 1 wherein the chemotherapy is for prophylactic treatment.

Given the indefinite nature of claims 2 and 7, it is assumed for examination purposes that compounds that bind to Topo II and inhibit its activity or that bind to HSP90 and inhibit its activity are not required to be competitive or allosteric inhibitors and that the claims are inclusive of any compound that that binds to Topo II or HSP90 and inhibits their activity.

It is noted that the specification teaches that etoposide is a derivative of podophyllotoxin, see 3rd line from the bottom of p. 7.

Bilodeau et al. teach treating and preventing lung adenocarcinoma and small cell lung cancer with a combination of chemotherapeutics comprising, 17-(allylamino)-17-demethoxygeldanamycin/17-AAG and etoposide, where they are administered contemporaneously or sequentially, see col. 2, lines 33-45, col .7, lines 5-17, col.14, lines 5-15, col. 15, lines 7-31, col. 19, lines 13-29 and lines 43-65.

Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61) teaches that 17-AAG is a compound that binds and inhibits HSP-90 and competes for nucleotide binding to HSP90, see p.s56-s57.

Holland-Frei (Cancer Medicine 6, 2003, BC Decker) teaches that etoposide binds and inhibits Topo II.

Although Bilodeau et al. does not teach that etoposide binds to TOPO II and inhibits its activity and 17-AAG binds to HSP90 and inhibits its activity, the product of the prior art comprises the same product as used in the claimed method, that is etoposide and 17-AAG, thus the claimed method using the claimed products is anticipated because the product used in the prior art method will inherently be a compound that binds to TOPO II and inhibits its activity or binds to HSP90 and inhibits its activity because Neckers and Holland-Frei teach that these are inherent properties of etoposide and 17-AAG. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993) and In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Medline Plus teaches that there are three kinds of non-small cell lung cancer including lung adenocarcinomas. Although Bilodeau et al. does not specifically teach non-small cell lung carcinomas, given that Bilodeau et al. teach treating lung adenocarcinoma, Fraley et al. inherently teach a method of treating non-small cell lung carcinoma. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993) and In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

12. Claims 1-3, 7-9, 11-13, 16 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Fraley et al. (US Patent No. 6,306,874, October 23, 2001) as evidenced by Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61) and Holland-Frei (Cancer Medicine 6, 2003, BC Decker).

The claims are as set forth above.

Given the indefinite nature of claims 2 and 7, it is assumed for examination purposes that compounds that bind to Topo II and inhibit its activity or that bind to HSP90 and inhibit its activity are not required to be competitive or allosteric inhibitors and that the claims are inclusive of any compound that that binds to Topo II or HSP90 and inhibits their activity.

It is noted that the specification teaches that etoposide is a derivative of podophyllotoxin, see 3rd line from the bottom of p. 7.

Fraley et al. teach treating and preventing lung adenocarcinoma and small cell lung cancer with a combination of chemotherapeutics comprising, 17-(allylamino)-17-demethoxygeldanamycin/17-AAG and etoposide, where they are administered contemporaneously or sequentially, see col. 2, lines 33-45, col .8, lines 41-59, col. 21, lines 24-49, col. 25 lines 47-64, and col. 26, lines 10-26.

Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61) teaches that 17-AAG is a compound that binds and inhibits HSP-90 and competes for nucleotide binding to HSP90, see p.s56-s57.

Holland-Frei (Cancer Medicine 6, 2003, BC Decker) teaches that etoposide binds and inhibits Topo II.

Although Fraley et al. does not teach that etoposide binds to TOPO II and inhibits its activity and 17-AAG binds to HSP90 and inhibits its activity, the product of the prior art comprises the same product as used in the claimed method, that is etoposide and 17-AAG, thus the claimed method using the claimed products is anticipated because the product used in the prior art method will inherently be a compound that binds to TOPO II and inhibits its activity or

binds to HSP90 and inhibits its activity because Neckers and Holland-Frei teach that these are inherent properties of etoposide and 17-AAG. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993) and In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

Medline Plus teaches that there are three kinds of non-small cell lung cancer including lung adenocarcinomas. Although Fraley et al. does not specifically teach non-small cell lung carcinomas, given that Fraley et al teach treating lung adenocarcinoma, Fraley et al. inherently teach a method of treating non-small cell lung carcinoma. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993) and In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

13. Claims 1-3, 7-9, 11-12, and16 are rejected under 35 U.S.C. 102(b) as being anticipated Neckers (Trends in Molecular Med. 25 March 2002, 4: S55-S61, IDS) as evidenced by Holland-Frei (Cancer Medicine 6, 2003, BC Decker).

The claims are as set forth above.

Given the indefinite nature of claims 2 and 7, it is assumed for examination purposes that compounds that bind to Topo II and inhibit its activity or that bind to HSP90 and inhibit its activity are not required to be competitive or allosteric inhibitors and that the claims are inclusive of any compound that that binds to Topo II or HSP90 and inhibits their activity.

It is noted that the specification teaches that etoposide is a derivative of podophyllotoxin, see 3rd line from the bottom of p. 7.

Neckers teaches that 17-AAG is a compound that binds and inhibits HSP-90 and competes for nucleotide binding to HSP90, see p. s56-s57. Neckers teaches that 17-AAG in combination with taxol reduced tumor growth and increased survival in mice bearing small cell lung tumors, see p. S59 left. col. Neckers teaches that it is reasonable to test 17-AAG and

etoposide in vivo in tumors overexpressing Erb-B2, such as small cell lung cancer because ErbB2 is reduced by 17-AAG treatment of small cell lung cancer tumors, see p. S59 left. col. Thus Neckers teaches a method of administering the 17-AAG and etoposide

Holland-Frei (Cancer Medicine 6, 2003, BC Decker) teaches that etoposide binds and inhibits Topo II.

Although Neckers does not teach that etoposide binds to TOPO II and inhibits its activity, the product of the prior art comprises the same product as used in the claimed method, that is etoposide, thus the claimed method using the claimed products is anticipated because the product used in the method will inherently be a compound that binds to TOPO II and inhibits its activity because Holland-Frei teaches that these are inherent properties. Additionally, although Neckers doe not teach whether or not 17-AAG and etoposide would be administered contemporaneously or sequentially, given that these are the only possible options of administering two compounds, the prior art method would inherently be one of administering the 17-AAG and etoposide contemporaneously or sequentially. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993) and In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

14. No claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J. Reddig/
Examiner
Art Unit 1642

Susan Ungar

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR